UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/501,179	02/10/2000	Zheng-Pin Wang	1887.0060002/RWE/KKV	3508

7590 03/02/2004

Sterne Kessler Goldstein & Fox PLLC
Attorneys at Law
Suite 600
1100 New York Avenue NW
Washington, DC 20005-3934

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	19

DATE MAILED: 03/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/501,179	WANG ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *Dec 18, 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-11,13,15-17,19,21 and 23-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-11,13,15-17,19,21 and 23-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 12, 14, 18 and 20 have been canceled. Claims 1, 3-6, 8, 10, 11, 15, 19, 21 and 23 have been amended. Claims 1-11, 13, 15-17, 19, 21 and 23-28 are pending and under consideration.

2. Sections of Title 35, US Code not found in this Office action can be found in a previous Office action.

3. Claims 2, 4, 7, 10, 11, 21, 23-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 4 recite "large" cancer cell. The term "large" in claim 2 and 4 is a relative term which renders the claim indefinite. The term "large cancer cell" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification states on page 12, lines 10-13 that "In particular these cells have a diameter of about 20 to about 50 micrometers, and more specifically about 30 to about 50 micrometers". The specification is therefore setting out preferred embodiments of "large" cancer cells but this does not constitute a limiting definition for the term :large" in reference to said cancer cells.

Claim 2 recites "large nucleus". The term "large nucleus" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 2 and 4 recite "fragile...cancer cell". It is unclear how a "fragile large cancer cell" has the quality of being a "fragile large cancer cell" rather than a "large cancer cell".

Claim 7 recites "late-stage" dying cell. The term "late stage" is a relative term. It is unclear how to determine the difference between the "late stage" dying cell of claims 7 and a nucleated terminal cell which dying.

Claim 10 recites "small" proliferative cell. The term "small" in claim 10 is a relative term which renders the claim indefinite. The term "small" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of

ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is noted that page 14, lines 14-15 state "The existence of these dividing cells may serve as evidence that circulating cancer cells are capable of survival and can undergo mitosis which in the circulation.. This subclass comprises two types of cells that are about 25 to 35 micrometers in diameter". This discussion in the specification does not serve a limitation for the term "small" proliferative cell.

Claim 11 recites the term "microtumor". The specification states on page 14, lines 27-29 that "this type of cell begins as a cluster of 3 to 4 cells and has the potential, if the environment permits, to grow into a microtumor comprising 5 or more cells". This does not constitute a limiting definition for the term "microtumor". Thus, the claims are rendered vague and indefinite because the metes and bounds of what constitutes a "microtumor" is undefined.

Claim 21 is vague and indefinite in the recitation of "comparing the number or classes of said isolated cancer cells to the number or classes of said second isolated cancer cells". The method step refers to comparing the number of cancer cells in the alternative to comparing the classes of said first isolated cancer cells. It is unclear how the method wherein section (e) is carried out by determining the number of cancer cells rather than the classes of the isolated cancer cells related to section (b) wherein the isolated cancer cells must be classified.

Claim 25 recites "for a period of time". The metes and bounds of what constitutes the range of "a period of time" is not defined by the specification or the claims.

4. Claims 1-11, 13, 15-17, 19, 21 and 23-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for circulating cancer cells in the blood which are epithelial, does not reasonably provide enablement for circulating non-epithelial cancer cells or circulating epithelial cells which are not in the blood. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims..

The claims are broadly drawn to encompass all forms of circulating cancer cells including sarcomas, mesotheliomas, and hematopoietic malignancies such as leukemias and lymphomas. The specification teaches specific cell sizes in order to classify circulating tumor cells as to proliferative or dying. The specification sets forth the preferred embodiments of

breast and prostate cancer cells in the blood of patients (Example 1, beginning on page 34). The specification does not provide any teaches for the specific dimensions or other characteristic to differentiate between circulating non-epithelial cancer cells which are proliferative versus non-proliferative. The art recognizes that most malignant cells which are released from a tumor die without forming a focus of metastatic cells which successfully colonize another body site. The art teaches that in order for a metastasis to be established , circulating neoplastic cells must adhere to the vascular endothelium, and that this adherence process is affected by factors such as cell or clump size, diameter of the vascular capillary in which the cells are lodged and the stickiness of the capillary wall which is determined by factors in the blood (LaVia, Principles of Pathbiology, 1975, page 213, second full paragraph). The art also recognizes that many neoplasms spread by direct extension or metastasis through the lymphatic channels (LaVia, page 213, first sentence of the last full paragraph). Thus, the specification has not enabled the scope of the claims with respect to body fluid because spreading cancer cells within a lymph node could not be considered to be "circulating" cancer cells which is required by the claim. Further, one of skill in the art would not expect that every cancer cell type, be it derived from a carcinoma or a sarcoma or a primitive hematopoietic stem cell, would conform to the size classification used for breast and prostate cells which are carcinoma cells derived from epithelial cells (i.e. non-proliferative large cancer cells of about 20 to about 50 micrometers versus small proliferative cancer cells of about 25 to 35 micrometers in diameter as taught in the specification. The scope of the claims must be commensurate with the scope of the enablement set forth, and given the lack of specific teachings in the specification on the cellular dimensions associated with all possible types of cancer cells in the proliferative or non-proliferative state, one of skill in the art would be subject to undue experimentation in order to practice the broadly claimed method.

5. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treatment consisting of surgery, radiation, hormone therapy and therapeutic agent administration, does not reasonably provide enablement for medical procedure of gene therapy. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and us the invention commensurate in scope with these claims.

Claim 26 carries the specific limitation of "gene therapy" to the method of claim 21. In order to practice claim 26 to the full scope of the claims, the medical procedure of gene therapy must be enabled. However, the state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available

vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that in 1995 current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claim 26 to the extent that it reads on gene therapy.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 11, 13, 15-17, 21 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rimm et al (U.S. 6,197,523) in view of LaVia et al (Principles of Pathobiology, 1975, page 213) and Maggi et al (Cangro, 1963, Vol. 16, pp. 169-188) and Pavone et al (Clinical Ostetrica E Ginecologica, 1963, Vol. 65, pp. 475-480).

Claim 1 is drawn to a method of classifying cancer cells in a body fluid sample of a patient with cancer or a patient suspected of having cancer, said method comprising isolating circulating cancer cells from said body fluid sample of said patient, and classifying said isolated cancer cells as terminal cells or proliferative cells by cytological and morphological analyses using fluorescence microscopy. claim 8 embodies the method of claim 1 wherein at least one cancer cell is a proliferative cell. Claim 11 embodies the method of claim 1 wherein at least three of said isolated cancer cells are in the form of a microtumor. Claim 13 embodies the method of claim 1 wherein the cancer cells are epithelial cells. Claim 15 embodies the method of claim 1 wherein said body fluid is blood. Claim 16 embodies the method of claim 1 wherein the body fluid sample is a concentrated body fluid sample, Claim 17 specifies the sample of claim 16 is a leukapheresis fraction.

Claim 21 is drawn to a method of determining the efficacy of a medical procedure for the treatment of cancer in patients said method comprising conducting a first isolation of circulating cancer dells in a body fluid sample of the patient; classifying said isolated cancer cells as terminal cells or proliferative cells by cytological and morphological analysis using fluorescent microscopy; conducting a second isolation of circulating cancer cells in a body fluid sample of the patient; repeating (b) on said second isolated cancer cells and comprising the number or classes of said first isolated cancer cells to the number or classes or said second isolated cancer cells , wherein he fist isolation is conducted before the administration of the medical procedure and the second isolation is conducted after the administration of the medical procedure, thereby determining the efficacy of said medical procedure. Claim 23 embodies the method of claim 21 wherein the presence of more terminal cells in the second isolation than in the first isolation is indicative of a positive response to the medical procedure. Claim 24 embodies the method of claim 21 wherein the presence of more proliferative cells in the second isolation than in the first

isolation is indicative of a negative response to the medical procedure. Claim 25 embodies the method of claim 21 wherein an increase or no change in the level of circulating cells during or after terminating the medical procedure for a period of time. Claim 26 embodies the method of claim 21 wherein said medical procedure is selected from the group consisting of surgery, radiation, hormone therapy, gene therapy and therapeutic agent administration, or a combination thereof. Claims 27 and 28 embody the method of any one of claim 1, 19 and 21 wherein said cancer cells are breast cancer cells and prostate cancer cells, respectively.

Rimm et al teach a method of isolating circulating tumor cells of epithelial origin from the blood of patients as exemplified by prostate and breast cancer cells (column 6, lines 7-15). Rimm et al teach that these isolated cells can be morphologically and colormetrically identified in situ in the blood sample (column 6, lines 15-18). Rimm et al teach that the preliminary morphological visual analysis or the photometric epitomic analysis is performed in the vicinity of the platelet layer or the expanded buffy coat in the blood sample (column 6, lines 7-10), thus fulfilling the specific embodiments of leukapherisis fraction. Rimm et al teach that the detection of nucleated cells which are suspected to be cancerous or of hematological progenitor origin that are found in the centrifuged blood sample in the vicinity of the platelet layer can be based upon differential staining of the suspected cells as the result of the presence and or absence of surface epitopes known to be present on most epithelial cells and are known to be absent on normal circulating blood cells. Rimm et al suggest the use of fluorophores for the detectable label (column 5, lines 37-52). Rimm et al teach that morphometric criteria which can be visualized in the blood sample in situ in the tube assembly include: intracellular nuclear/cytoplasmic ratios; intracellular nuclear size and shape; intracellular nuclear chromatin pattern; the thickness and size of the nuclear membrane; and the number and size of nucleoli and that epithelial cancer cells and hematologic progenitor cells layer out in the centrifuged anticoagulated whole blood sample by density, rather than by sedimenting out in the blood sample by size (column 12, lines 20-30). Rimm et al teach that the aforesaid procedures and apparatus can be used to screen patients for the presence or absence of cancer cells; can be used to assess staging of a malignant tumor; can be used to assess the effectiveness of chemotherapy on patients being treated for cancer (column 12, lines 61-65), thus rendering obvious the specific embodiment of claims 21 and 23-28, drawn to determining the efficacy of a medical procedure. Rimm et al do not specifically teach

fluorescence microscopy, however, Rimm et al do teach the use of fluorescent labels and immunofluorescent techniques as fluorescent microscopy is routine in the art for the detection of cancer cells in the blood as exemplified by the citations of Maggi and Schultis (Cangro, 1963, Vol. 16, pp. 169-188) and Pavone and Rolfini (Clinical Ostertrica E Ginecologica, 1963, Vol. 65, pp. 475-480). Rimm et al .do not specifically teach the classification of the isolated tumor cells into terminal or proliferative cells.

LaVia et al teach that most individual neoplastic cells that enter the bloodstream die without forming a new nidus of malignant disease sand that certain conditions must be optimal for the metastasis to be established. (page 213m second full paragraph). One of skill in the art would reasonably conclude that individual neoplastic cells that fail to find the proper environment will continue to circulate and eventually die, and thus these dead or dying cells will be ciculating in combination with other neoplastic cells which are viable.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to classify the tumor cells as dying or proliferative. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of LaVia et al on the death of the majority of metastatic cells which fail to find an appropriate location for the establishment of a metastatic lesion. One of skill in the art would reasonably conclude that a patient having viable circulating tumor cells will be at a higher risk for developing metastatic disease than a patient having a lower level of viable circulating tumor cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571)272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
Primary Examiner, Art Unit 1642
02/25/04

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER

***